ORIGINAL STUDY

THE ACIDOSIS – MALNUTRITION – INFLAMMATION ASSOCIATION: CLINICAL IMPLICATIONS ON THE MAINTENANCE DIALYSIS PATIENTS

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ABSTRACT

After the incredible results obtained with eritropoiesis-stimulating agents and vitamin D analogues in the amelioration of the duration and quality of life for the chronic renal patients, a new pathogenic complex draws the attention of nephrologists, cardiologists, internists, diabetes specialists and family doctors that are treating chronically dialysed patients: MICS (malnutrition inflammation complex syndrome). This concept describes the phisiopathological bind between chronic inflammation and the nutritional status by linking them through hypercatabolism and metabolic acidosis. This study refers to the unfortunate influence of persistent metabolic acidosis on the morbidity and mortality rates of maintenance dialysis patients: acidosis enhances catabolism and inhibits anabolism by associating itself with severe nutritional deficits, stimulating the pro-inflammatory factors and promotes proteolysis.

1. Introduction

Chronic renal insufficiency represents a complex pathological ensemble in which the incapacity to excrete nitrogenate compounds and hidric excess represents only a part of the consequences of renal function affliction, with dialysis correction. Some other important functions of the diseased kidney found therapies that supplement them: eritropoiesis stimulating-agents to compensate secondary anemia, vitamin D analogues to optimize the phospho-calcic metabolism, PTH levels and to correct renal bone dystrophy [1]. Over the last years, a new pathogenic complex draws the attention of nephrologists, but also of internists, cardiologists, diabetes specialists and family doctors that are treating chronic renal insufficiency patients: MICS (malnutrition inflammation complex syndrome). [2-4].

This concept describes the physiopathological bound between chronic inflammation and nutritional status, with the help of enhanced catabolism and metabolic acidosis [5-7]. Patients with malnutrition

have a chronic inflammatory status and high scores for morbidity and mortality in dialysis statistics [8,9].

To investigate the link between chronic acidosis state and the magnitude of the inflammation and to correlate these with malnutrition we bring a prospective non-interventional study in maintenance dialysis patients.

2. Material and methods

The study lasted 12 months and comprised 192 patients that were under chronic renal correction in the <HS Dialysis Clinic "Sfantul Ioan" Bucharest>, after trialing according to the standards imposed by this study.

Selection criteria: patients suffering from chronic kidney disease (BCR) stage 5 K/DOQT- chronic terminal disease- chronically hemodialysed or chronic ambulatory peritoneal dialysis.

Exclusion criteria: patients had other severe illnesses (comorbididies) that could have severely affected their life span – cardiac insufficiency, hepatic or respiratory severe insufficiency, malign tumors.

The patient batch was made up of 20 peritoneal dialysed patients and 164 chronic hemodialysed. The demographic characteristics of the patients are presented below (table I):

Table I. *Patients distribution*

	HD Batch		**DP Batch**	
Age average	41,3 years		67,2 years	
Genre distribution	93 men	71 women	12 men	16 women
Dialysis time span	54 months		25 months	
Number of initiations durring study	35		21	

The methodology of this study consisted in the monitoring and registering the interested biological constants:

-Serum bicarbonate at the beginning of dialysis (RApreD) to correctly assess the acid-base balance;
-Albuminemia and the SGA test – to appreciate nutritional status;
-CRP level (C reactive protein) – in order to correctly asses inflammatory status.

Depending on the RApreD, we divided the patients into batches depending on their levels: severe acidosis, moderate acidosis, acid-base balanced, and we investigated nutritional status and inflamatory status in different preD-AR groupes of values.

3. Results

Serum bicarbonate or pre-dialysis plasma bicarbonate in chronic hemodialysed patients: *RApreD.*

This is the gold-standard in measurement parameters of metabolic acidosis in chronic dialysed patients; it is done monthly before starting hemodialysis, amidst the monthly tests that are done to asses these patients progress.

Monthly RApreD (rezerva alcalina predialitica) was analyzed both as an average value of the batch at every dialysis and as an annual average of RA for every patient.

The monthly levels in the dialysed batch had a wide spread, from patients with levels of under 18 mEq/l to patients with over 30 mEq/l. the lowest level on the acidosis scale was 7mEq/l on a patient in which hemodialysis was instituted in the Emergency Room, in a case of severe acute progress in his chronic renal insufficiency.

To globally describe each patient from the levels of RA point of view, the most correct and "complete method was considered the annual RApreD values for each and every patient separately.

From figure 1, we can observe that most patients – 59.92% - have RA values found in the "metabolic acidosis area" under 22 mEq/l.
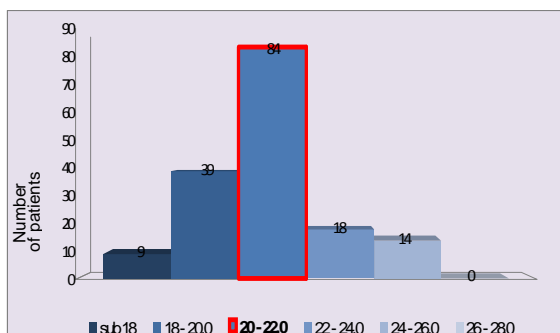

Figure 1. *The distribution of average RApreD levels in RApreD groups*

The interrelation between markers of inflammation in different RA groups

The amount of CRP in different RA groups

After the 4 CRP determinations in the fist year of study we calculated the average amount per patient and ve divided the batch of dialysed patients in 3 CRP-amount groupes: under 6 mg/l, 6-20 mg/l, and over 20 mg/l. The aftermath was afterwards analysed and centralised in pre D–AR values:

- CRP values under 6 mg/l (117 patients)
- CRP values 6-20 mg /l (29 patients)
- CRP values over 20 mg/ l (18 patients). (figure 2)
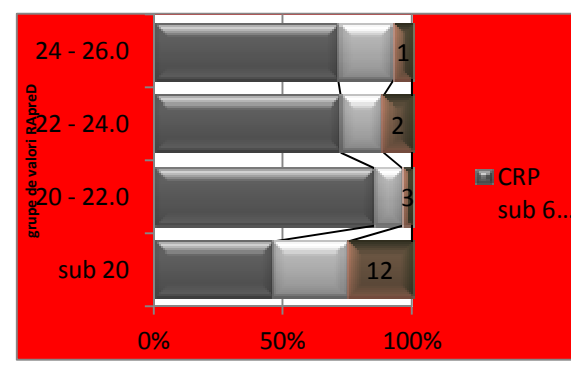
Figure 2. *CRP values in RApreD groups*

We have noticed that in the batch of patients that have the highest CRP levels are also the most

RApreD patients with under 20mEq/l. Also these patients have the highest SGA levels – patients suffering from severe malnutrition.

This sagregation shows the „malnutrition – inflamation - acidosis complex", an extremely unfortunate joinder which determines a malevolent progress of hemodialysed patients that suffer from it. These patients usually have a multi-factorial situation: severe anemia with resiliency to the eritropoiesis stimulation therapy, and high morbidity with a high mortality risk.

This is a double way band: not only is the chronic inflamation determining hypercatabolism, the drop in anabolism and high output of acids, but also acidosis favourises inflamation by incereasing the action of ubiquitin and the branched-chain keto acids dehidrogenase (BCKAD).

Through statistic analysis, we can show that there is a larger procentual number of patients with RApreD under 20 mEq/l in the group with CRP levels over 20 mg/l (Z= 2,76 > 1,28).

RA correlation with nutritional status markers

The amount of plasma albumin in different AR groups

The average amount of albumin within a batch of RApreD patients with under 20 mEq/l values, was 3.96 g% compared to the average amount of 4.18 g% found in a batch of RApreD patients with over 22 mEq/l. The slight decrease that we observe in RApreD patients with 24-26 mEq/l isn't accompanied by the same occurrence on the SGA scale and we can base this observation on the hypervolemia measured in these patients (that also have metabolic alkalosis after dialysis) (figure 3).

SGA in different RA groups

After analyzing the SGA results, 46 patients (28.1%) were diagnosed with malnutrition in different stages. This procentual number has greater importance than the one corresponding to the diagnosis based on the value of plasma albumin,

because the associated illnesses of every patient are taken into account. The apportionment of SGA indicating values, in pre-dialysis RA groups of

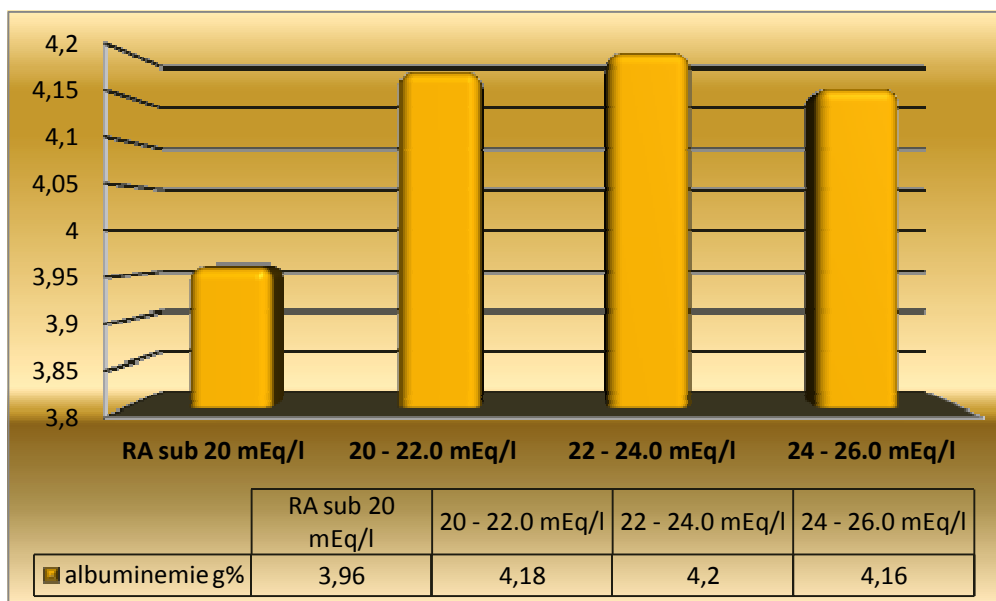values, have emphasized differences that are worth analyzing (Figure 4).

	RA sub 20 mEq/l	20 - 22.0 mEq/l	22 - 24.0 mEq/l	24 - 26.0 mEq/l
albuminemie g%	3,96	4,18	4,2	4,16

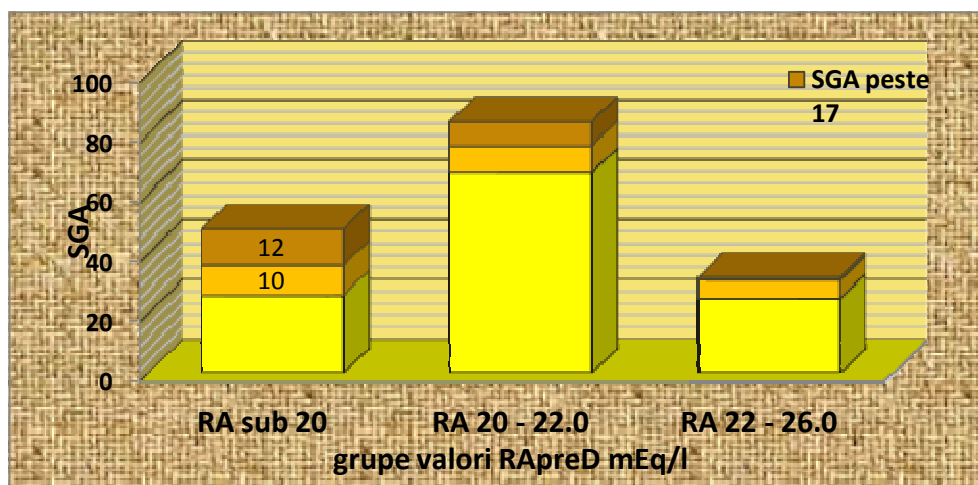**Figure 3.** *Serum albumin values in RApreD groups*

Figure 4. *The distribution of SGA values in preD-AR groups of values*

We have captured data concerning SGA values corresponding to malnutrition in 22 patients of the 48 with AR values under 20mEq/l (45.8%), to 17 patients (20.2%) of the 84 with AR between 20-22 mEq/l and to 7 of the 32 patients with an AR between 22 and 26 mEq/l (21.8%).

Statistically analyzing, we calculated

$$z_{1-\alpha} = z_{0,90} = 1,28$$

and Z = 4,46 . 1,28   that is found in the rejection area: the number of patients suffering from malnutrition in the "under 20 AR   " group is significantly larger than in all other groupes.

The level of albumine in the "under 20mEq/l AR" groupes is significantly lower (statistically), than the average of all the other groupes of patients, which are not so different from each other.

4. Discussions

This study shows that the patients who arround the year had an average level of under 20 mEq/l preD-AR, were often in the group of patients with severe malnutrition, they have a lower nutritional score than the rest of the preD-AR groupes, and had significantly higher levels of CRP (modified inflamatory status). Moderately-severe metabolic acidosis is usually asociated with inflamation and malnutrition, strenghtening each other all the time.

The way in which these entities relate is not clear enough. It is certain the hypercatabolic efect of persistent metabolic acidosis; low sanguin pH determines negative nitrogen balance in CRF patients and healthy individuals. It increses protein catabolism, decreases protein synthesis and increase insulin resistance.

Activation due to the hyperactivation of ubiquitin-protease ATP-dependant and the branched keto-acid dehydrogenase, in acidosis. It is presumed that these enzymes would also produce endocrine abnormalities like: the resistance to insulin, the decreasing of circulant leptine levels, and the boosting of pro-inflamatory citokin levels.

5. Conclusions

This study gives just one of the explanations of how unfortunate the influence of persistent metabolic acidosis is on the morbidity and mortality of chronic hemodialysed patients: acidosis favours hypercatabolism and inhibits anabolism, by associating with malnutrition. The inflamatory status is both a consequence of malnutrition and of metabolic acidosis (by stimulating pro-inflammatory citokines). This vicious circle is closed with the hypercatabolic efect of chronic inflammation. In order to properly act towards the breaking of this pathogenic chain, we will have to tend to its every link. As the treatment of chronic metabolic acidosis has received much less atention than treatment of other ESDR complications (anemia, hyperphosphatemia, hyperparathyroidism), the result of this study comes to support the propper diagnossis and treatment of chronic metabolic acidosis in chronic dialysed patient.

References

1. **Rădulescu D., David C., Ciocâlteu A., Mocanu B., Costache D.M:** cap. 16 Insuficienta renala cronica in Tratat de Nefrologie - Al. Ciocâlteu, Ed. Național: 2006, 593-642,
2. **Wu D.Y., Shinaberg C.S., Regidor D.L., McAllister C.J., Kopple J.D., Kalantar-Zadeh K.:** Association between serum bicarbonate and death in hemodialysis patients: it is better to be acidotic or alkalotic? Clin J Am Soc Nephrol. 2006 ian; 1(1) 70-8
3. **Kalantar-Zadeh K., Mehrotra R., Fouque D., Kopple J.D.:** Metabolic acidosis and malnutrition-inflamation complex syndrome in chronic renal failure. Semin Dial 2004, 17:445-465
4. **Lin S.H., Lin Y.F., Chin H.M., Wu C.C.:** Must metabolic acidosis be associated with malnutrition in hemodialysed patients? Nephrol Dial Transplant 2002, 17: 2006-2010
5. **Mitch WE, Medina R, Grieber S, May RC, England BK, Price SR, Bailey JL, Goldberg AL**: Metabolic acidosis stimulates muscle protein degradation by activating the adenosine triphosphate-dependent pathway involving ubiquitin and proteasomes. *J Clin Invest* 1994, 93: 2127-2133.
6. **Checheriță I.A., F.Turcu, R.F.Dragomirescu, Al.Ciocalteu:** Chronic complications in hemodialysis-correlations with primary renal disease. *Romanian Journal of Morphology and Embryology,* 2009,.50,.4
7. **Owen WF, Lowrie EG:** C-reactive protein as an outcome predictor for maintenance hemodialysis patients. *Kidney Int* 1998, 54:627-636,
8. **Acchiardo S.R., Moore l.W., Latour P.A.:** Malnutrition as a main factor in morbidity and mortality of hemodialysis patients. Kidney Int. 1983; 24(16):99-203
9. **Lowrie E.G., Lew N.L.:** Commonly measured laboratory variables in hemodialysis patients: Relationship among them and to death risk. Semin Nephrol. 1992; 12:276-83